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בקשה לפטנט
Application for Patent

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מספר: Number	130324
תאריך: Date	07 -06- 1999
הוקדם/נדחה Ante/Post-dated	

אני, (שם המבקש, מענו ולגבי גוף מאוגד - מקום התאגדותו)
(Name and address of applicant, and in case of body corporate-place of incorporation)

ידע חברה למחקר ופיתוח בע"מ, חברה ישראלית, ליד מכון ויצמן למדע, ת.ד. 95, רחובות 76100
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(באנגלית) (English)
Pharmaceutical compositions comprising iron chelators for the treatment of neurodegenerative disorders and some novel iron chelators

מבקש בזאת כי ינתן לי עליה פטנט hereby apply for a patent to be granted to me in respect thereof.

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מבקשת פטנט from Application	*לבקשה/לפטנט to Patent/Appl.	מספר/סימן Number/Mark	תאריך Date	מדינת האגוד Convention Country
מס' No.....	מס' No.....			
מיום dated.....	מיום dated.....			
* יפוי כח: כללי / מיוחד - רצוף בזה / עוד יוגש P.O.A.: general / individual-attached / to be filed later -				
הוגש בעניין filed in 110696 case				
המען למסירת מסמכים בישראל Address for Service in Israel Paulina Ben-Ami Yeda Research & Development Co. Ltd. P.O.Box 95, Rehovot 76100				
חתימת המבקש Signature of Applicant For the Applicants, Paulina Ben-Ami Paulina Ben-Ami Patent Attorney 9956		היום This 06 בחודש of יוני שנת 1999 of the year		

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9842

Pharmaceutical compositions comprising iron chelators for the treatment of neurodegenerative disorders and some novel iron chelators

תכשירי רוקחות המכילים קלטורים של ברזל לטיפול במחלות עצבים וקלטורים של ברזל חדשים מסויימים

Yeda Research and Development Co. Ltd.
and
Technion Research and Development Foundation Ltd.

Inventors: Abraham Warshawsky, Moussa B.H. Youdim,
Dorit Ben-Shachar

ידע חברה למחקר ופתוח בע"מ
ומוסד הטכניון למחקר ופתוח בע"מ

ממציאים: אברהם ורשבסקי, משה ב.ח. יודעים,
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FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions comprising as active ingredients compounds that act as neuroprotective iron chelators and are suitable for the treatment of neurodegenerative disorders such as Parkinson's disease, Alzheimer-type dementia and stroke. The invention further relates to certain novel iron chelators of the type described in the specification.

BACKGROUND OF THE INVENTION

Parkinson's disease is a progressive neurodegeneration of the melanized dopaminergic neurons in the substantia nigra. It is clinically characterized mainly by akinesia, bradykinesia and tremor at rest. Postmortem studies on brains from parkinsonian patients suggest the involvement of oxygen free radical-induced oxidative stress which results in lipid peroxidation of cell membranes, followed by increased membrane fluidity and finally cell death.

Normally dopamine (DA) is metabolized by either monoamine oxidase or by autooxidation. Both ways lead to an excess of toxic oxygen species, such as H_2O_2, which in the presence of a transient metal, such as iron, will produce cytotoxic oxygen free radicals, e.g. superoxide and hydroxyl free radicals. The brain, like all other tissues, protects itself against the deleterious effects of oxygen free radicals by specific protective enzymes such as glutathione peroxidase, catalase and superoxide dismutase and by relatively high amounts of glutathione and ascorbate. In

addition, iron is bound to high molecular weight proteins such as ferritin, hemosiderin and transferrin, or to low molecular weight molecules such as ADP, ATP, catechol and probably also melanin, and its amount in the brain is strictly conserved by the blood brain barrier (BBB).

In Parkinson's disease, the brain defensive mechanisms against the formation of cytotoxic oxygen free radicals are defective. In the substantia nigra of parkinsonian brains there are reductions in activities of superoxide dismutase and glutathione peroxidase and reduced tissue contents of glutathione and ascorbate. Moreover, iron concentrations are significantly elevated in parkinsonian substantia nigra pars compacta within the melanized dopamine neurons. These conditions favour liberation of free cytotoxic radicals, which can cause among other things release of intracellular calcium and lipid peroxidation resulting in neuronal death. Indeed an increase in basal lipid peroxidation in the substantia nigra of parkinsonian patients has been detected.

Iron alone or iron decompartmentalized from its binding site by a neurotoxin, e.g. the dopaminergic neurotoxin 6-hydroxydopamine (6-OHDA), may induce oxidative stress and neurodegeneration, as evidenced in previous studies of the inventors in which intranigral administration of iron induced "Parkinsonism" in rats and the iron chelator desferrioxamine protected the rats against 6-OHDA-induced lesions of nigrostrial dopamine neurons (D. Ben-Shachar and M.B.H. Youdim, 1991, J. Neurochem. 56: 1441-4). It has thus been suggested that treatment or retardation of the process of dopaminergic neurodegeneration in the substantia nigra may be affected by iron chelators capable

of crossing the blood brain barrier in a fashion similar to chelators used in the treatment of Wilson's disease and iron overload in systemic organs.

This may be a new therapeutic approach for the treatment of Parkinson's disease that can be applied to other metal-associated neurological disorders such as tardive dyskinesia, Alzheimer's and Hallervorden-Spatz diseases.

Stroke is the third leading cause of death in the western world today, exceeded only by heart diseases and cancer. The overall prevalence of the disease is 0.5-0.8% of the population. Stroke is characterized by a sudden appearance of neurological disorders such as paralysis of limbs, speech and memory disorders, sight and hearing defects, etc, which result from a cerebrovascular damage.

Haemorrhage and ischemia are the two major causes of stroke. The impairment of normal blood supply to the brain is associated with a rapid damage to normal cell metabolism including impaired respiration and energy metabolism lactacidosis, impaired cellular calcium homeostasis release of excitatory neurotransmitters, elevated oxidative stress, formation of free radicals, etc. Ultimately these events lead to cerebral cell death and neurological disfunction.

Treatment of stroke is primarily surgical. Much effort is being invested in less agressive therapeutical intervention in the search for drugs which are capable to restore normal blood perfusion in the damaged area as well as drugs which are designed to overcome the above listed damaging events associated with cellular damage.

Oxidative stress and free radical formation play a major

role in tissue injury and cell death. These processes are catalysed by transient metal ions, mainly iron and copper. In the case of stroke, since vascular damage is involved, iron is available for the free radical formation, a process that could be prevented by iron chelators. Indeed, with lazaroides (21-amino steroids), known free radical scavengers, a significant improvement of local and global ischemia damages induced in animals has been achieved.

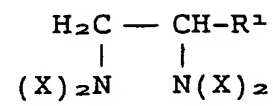
For the treatment of Parkinson's disease and probably other metal-associated neurological disorders and for the treatment of trauma and stroke and the secondary injuries which follow them, it would be highly desirable to find neuroselective iron chelators that cross the blood brain barrier.

SUMMARY OF THE INVENTION

It has now been found in accordance with the present invention that certain iron chelators which can cross the brain blood barrier are able to protect from neurodegenerative processes in the rat, thus making them suitable candidates for treatment of Parkinson's disease and for other metal-associated neurological disorders and for the treatment of trauma and stroke.

The present invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and as active ingredient a compound selected from the group consisting of:

(a) a compound of formula I:



(I)

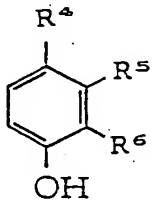
wherein

R^1 is a radical $-(CH_2)_n-CONR^2R^3$ wherein n is an integer from 1 to 20, R^2 is H or hydrocarbyl and R^3 is a hydrophobic radical, and

X is a radical - CH_2Y, wherein Y is a radical 3-acyl-4-hydroxyphenyl, 3-hydroxyiminoalkyl-4-hydroxyphenyl, or COOZ, wherein Z is H, alkyl, aryl or aralkyl,

and

(b) a compound of formula II:



(II)

wherein

R^4 is acyl, nitroalkyl, alkoxymethyl or $-CH_2NR^7R^8$, wherein R^7 and R^8 are H or alkyl or together with the N atom form a saturated or unsaturated 5-6 membered ring optionally containing a further heteroatom selected from N, O or S, the further N atom being optionally substituted, and

either R^5 is H and R^6 is acyl or hydroxyiminoalkyl or R^5 and R^6 together with the phenyl ring form a quinoline, a 1,2,3,4- tetrahydroquinoline or a perhydroquinoline ring, and

pharmaceutically acceptable salts of the compounds of formulas I and II.

The invention further relates to novel compounds of formulas I and II, excepting the compounds of formula II 5-formyl-8-quinolinol and 5-methoxymethyl-8-quinolinol.

In the compounds of formula I, R^1 is preferably a radical in which n is 2 to 4, most preferably 2. The term "hydrocarbyl" is used herein for the radical R^2 to refer to substituents that are saturated, unsaturated or aromatic, including but not being limited to C_1-C_8 alkyl, C_2-C_8 alkenyl and phenyl. The "hydrophobic" radicals as used herein for R^3 include, but are not limited to, radicals such as C_6-C_{20} alkyl, C_6-C_{20} alkenyl, C_5-C_{20} acyl, optionally substituted benzyloxycarbonyl, C_3-C_8 alkyloxycarbonyl, cycloalkyloxycarbonyl, aryloxycarbonyl, N-substituted amino(C_1-C_4)alkyl and 4-substituted-piperazinyl (C_1-C_4)alkyl.

Illustrative examples of hydrophobic radicals for R^3 include, but are not limited to, the following: saturated and unsaturated acyl groups, such as, for example, hexanoyl, octanoyl, lauroyl, palmitoyl, myristil, stearoyl, aracidyl, etc; benzyloxycarbonyl and substituted benzyloxycarbonyl, such as, for example, o- and p-chlorobenzyloxycarbonyl, 2,4- and 2,6-dichlorobenzyloxycarbonyl, etc; alkyloxycarbonyl, such as, for example, t-butyloxycarbonyl (Boc), t-amyloxycarbonyl, isopropyloxycarbonyl, etc; cycloalkyloxycarbonyl, such as, for example, cyclopentyl-oxycarbonyl, cyclohexyloxycarbonyl, adamantyloxycarbonyl (Adoc), etc.; aryloxycarbonyl, such as, for example, fluorenylmethyloxycarbonyl, etc.; 4-substituted-piperazinyl(C_1-C_4)alkyl, in which the 4-substituent is any of the hydrophobic groups mentioned above; and N-substituted amino(C_1-C_4)alkyl, in which the N-substituent is any of the hydrophobic

groups mentioned above.

The radical Y in the compounds of formula I is a group 3-acyl-4-hydroxyphenyl, in which the acyl is preferably C_2-C_6 acyl including, but not being limited to, acetyl, propionyl, butyryl, etc.; a group 3-hydroxyimino(C_2-C_6)alkyl-4-hydroxyphenyl, in which the alkyl may be ethyl, propyl, butyl, etc.; or a group COOZ in which Z is H, C_2-C_6 alkyl, aryl, such as phenyl, or aralkyl, such as benzyl.

In preferred embodiments of the invention in the compounds of formula I R^1 is a radical $-(CH_2)_2CONH(CH_2)_3NHCO_2CH_2C_6H_5$ or $-(CH_2)_2CONH(CH_2)_2$-(4-carbobenzoxy-)piperazinyl, and X is benzyloxy-carbonylmethyl, 3-acetyl-4-hydroxybenzyl or 3-(1-hydroxy-iminoethyl)-4-hydroxybenzyl. Examples are the compounds of formula I identified herein below in the Examples as SL-16, VK-11 and VK-12.

The compounds of formula II in which R^5 is H and R^6 is acyl or hydroxyiminoalkyl represent keto derivatives of phenol and their corresponding oximes. The acyl here is preferably C_2-C_6 saturated aliphatic acyl, such as, for example, acetyl, propionyl, butyryl, etc, and the alkyl is also C_2-C_6 alkyl, such as, for example, ethyl, propyl, butyl, etc.

In the compounds of formula II R^4 may be C_1-C_6 acyl, such as, for example, formyl, acetyl, propionyl, etc.; nitroalkyl, in which the alkyl group may be branched, such as, for example, 2-methyl-2-nitropropyl; C_1-C_6 alkoxymethyl, such as, for example methoxymethyl, ethoxymethyl, etc.; $-CH_2NR^7R^8$, in which R^7 and R^8 are both H, or one is H and the other is C_1-C_6 alkyl, or both R^7 and R^8 are alkyl, such as, for example aminomethyl, methlyamino-methyl, ethylaminomethyl, dimethylaminomethyl,

diethylaminomethyl, etc., or R^7 and R^8 together with the N-atom form a saturated or unsaturated 5-6 membered ring optionally containing a further heteroatom selected from N, O or S, the further N-atom being optionally substituted by C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxycarbonyl, such as, for example, R^4 is piperidinylmethyl, morpholinylmethyl, thiomorpholinylmethyl, 4-methylpiperazinylmethyl, 4-(2-hydroxyethyl)-piperazinylmethyl, 4-ethoxycarbonylpiperazinylmethyl, imidazolylmethyl, etc.

In a preferred embodiment, the compounds of formula II are phenol derivatives as represented by the compounds N-269 and N-275 herein in the Examples. In another preferred embodiment, the compounds of formula II are quinoline derivatives as represented by the compounds VK-5, VK-8, VK-28, VK-61, VK-62, VK-63, VK-64, VK-67, VK-68, VK-69 and VK-70 herein in the Examples. It is to be noted that the compounds VK-5 and VK-62 are not herein claimed as novel compounds.

The compounds of the invention are prepared by methods well-known to those of skill in the art of chemical synthesis. Some of these methods are illustrated herein the Examples. For the preparation of other compounds of formulas I and II, similar procedures known to those of skill in the art may be used.

The compounds of formulas I and II were found according to the present invention to prevent lipid peroxidation in brain homogenates *in vitro*.

The present invention thus provides pharmaceutical compositions, useful to prevent lipid peroxidation in the brain of mammals comprising an effective amount of a compound of formula I or II herein or of a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable

carrier.

In another aspect, the present invention provides the use of a compound of formula I or II herein or of a pharmaceutically acceptable salt thereof as neuroprotective iron chelators for the preparation of pharmaceutical compositions for the treatment of Parkinson's disease and stroke.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 shows the extent of lipid peroxidation in rat brain homogenates *in vitro* as measured by malondiadehyde (MDA) formation in the presence of 10^{-4} M $FeCl_3$ with or without 10^{-3}M chelator according to the invention (compounds N269, N275, N271, VK-12, VK-18, SL-16) and Desferal (desferrioxamine, known iron chelator).

Fig. 2 shows striatal dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) concentrations as a consequence of intracerebral injection of 6-OHDA (250 µg) to rats treated for 10 days with peripheral injection of phosphate buffer or the compound VK-28 (combination). Control group was injected intracerebral with saline instead of 6-OHDA.

Fig. 3 shows the extent of lipid peroxidation in rat brain homogenates *in vitro* as measured by MDA formation in the presence of 10^{-4}M $FeCl_3$ with or without 10^{-3}M of several chelators according to the invention and Desferal (DES).

DETAILED DESCRIPTION OF THE INVENTION

The iron chelator compounds of the invention are useful for the treatment of Parkinson's disease and probably other metal-associated neurological disorders and for the treatment of trauma

and stroke and the secondary injuries which follow them, by virtue of their ability to cross the blood brain barrier and to prevent lipid peroxidation in the brain, a process which leads to neuronal death.

The ability of the compounds of the invention to prevent lipid peroxidation in brain tissue was first screened in rat brain homogenates *in vitro* by a method involving malondialdehyde (MDA) formation which utilizes the procedure described by D. Ben-Shachar et al. (1991) J. Neurochem. 57: 1609-14. In this method, brain cortex homogenates are prepared in sucrose and incubated alone to determine basal lipid peroxidation, or incubated after the addition of $Fe_2(SO_4)_3$ and in the presence of the iron chelators to be tested. Lipid peroxidation is assayed by measurement of malondialdehyde (MDA) formation.

The ability of iron chelators to act as neuroprotectors was first demonstrated in an animal model of Parkinson's disease (intraventricular injection of 6-hydroxydopamine (6-OHDA)) using the iron chelator desferrioxamine (D. Ben-Shachar et al. (1991) J. Neurochem. 56: 1441-44). A selective increase in content of iron in the pars compacta of the substantia nigra has been implicated in the biochemical pathology of Parkinson's disease. Iron is thought to induce oxidative stress by liberation of oxygen free radicals from H_2O_2. Because 6-hydroxydopamine (6-OHDA) is thought to induce nigrostriatal dopaminergic neuronal lesions via metal-catalyzed free radical formation, the effect of the iron chelator desferrioxamine was investigated on 6-OHDA-induced dopaminergic neuron degeneration in the rat. Intracerebroventricular injection of 6-OHDA (250 μg) caused a 88, 79 and 70% reduction in striatal tissue content of dopamine (DA),

3-4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), respectively and a 2.5-fold increase in DA release as indicated by the HVA/DA ratio. Prior injection of desferrioxamine (130 ng and 13 ng, i.c.v.) resulted in a significant protection (~60% and 100%, respectively) against the 6-OHDA-induced reduction in striatal DA content and a normalization of DA release Dopaminergic-related behavioral responses, such as spontaneous movements in a novel environment and rearing, were significantly impaired in the 6-OHDA-treated group. By contrast, the desferrioxamine-pretreated rats exhibited almost normal behavioral responses. The ability of iron chelators to retard dopaminergic neurodegeneration in the substantia nigra may indicate a new therapeutic strategy in the treatment of Parkinson's disease.

The compounds of formula I and II of the present invention were injected to rats as described in D. Ben-Shachar et al. (1991) J. Neurochem. 56: 1441-44 and were shown to efficiently prevent the 6-OHDA-induced reduction in striatal dopamine and DOPAC concentrations in the rat.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be encapsulating material.

Liquid form pharmaceutical compositions include solutions, suspensions, and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other well-known suspending agents.

Preferably, the pharmaceutical composition is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for example, packeted tablets, capsules, and powders in vial or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself or it can be the appropriate number of any of these packaged forms.

In therapeutic use for the treatment of Parkinson's disease, the compounds utilized in the pharmaceutical method of this invention are administered to the patient at dosage levels of from 1 mg/Kg to 20 mg/Kg per day.

In therapeutic use for the treatment of stroke one or more dosages of from about 100 mg/Kg to about 500 mg/Kg of body weight are administered to the patient as soon as possible after the event.

The dosage, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of

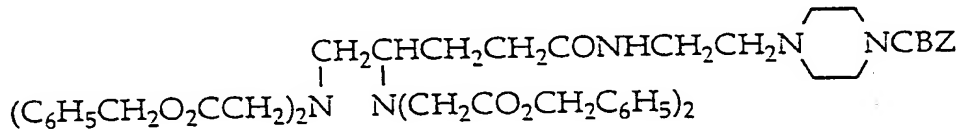
optimum dosages for a particular situation is within the skill of the art.

The following examples illustrate particular methods for preparing compounds in accordance with this invention. These examples are illustrative and are not to be read as limiting the scope of the invention as it is defined by the appended claims.

EXAMPLES

EXAMPLE 1

N-[2-(4-Carbobenzoxypiperazin-1-yl)ethyl]-4,5-bis[bis(benzyloxy carbonylmethyl)amino]valerylamide (SL-16)



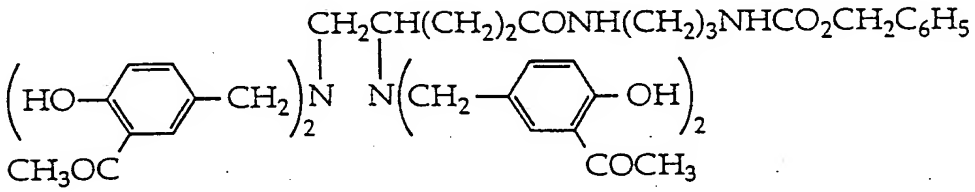
To a solution containing N-[2-(4-carbobenzoxypiperazin-1-yl)ethyl]-4,5-diaminovalerylamide (100mg, 0.27mmol) in 1ml CH_3CN (freshly distilled over P_2O_5), a mixture of tetramethylenenaphthalene diamine (0.306gr, 1.43mmol) and NaI (0.021gr, 0.14mmol) in 0.12ml freshly distilled CH_3CN was added. The mixture was heated slightly and stirred under a nitrogen atmosphere to dissolve all components. To this mixture, benzylbromoacetate was added (0.22ml, 0.328gr, 1.43mmol), and the mixture was refluxed at 96°C for 22 hrs under a nitrogen atmosphere.

Subsequently, the precipitate was filtered off and the solvent evaporated. $CHCl_3$ was then added to the filtrate, the solid filtered off once again, and the solvent evaporated. To remove excess benzylbromoacetate, the residual oil was then washed a few times with hexane, and finally dried under vacuum

to yield 300mg crude product. The product was then purified by flash chromatography, using $CHCl_3$:MeOH as the eluent. 47mg of the title product were obtained. No further purification was carried out.

EXAMPLE 2

N-(3-Benzyloxycarbonylaminopropyl)-4.5-bis[di(3-acetyl-4-hydroxy benzyl) amino] valerylamide N-271 (VK-11, VK-58)

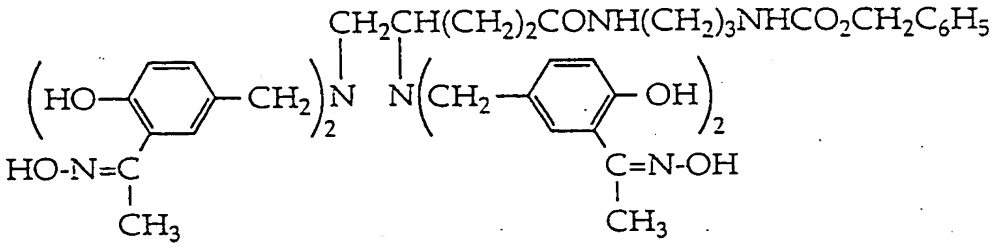


A suspension of 2-acetyl-4-chloromethylphenol (0.48 g; 2.6 mmol), N-(3-benzyloxycarbonylaminopropyl)-4,5-diaminovalerylamide (0.14 g; 0.43 mmol), diisopropyl(ethyl)amine (0.47 ml; 2.69 mmole) in DMF (10 ml) was stirred at room temperature for 24 hr. The mixture was evaporated to dryness. $CHCl_3$ (80 ml) was added to the residue, the reaction mixture was filtered off and the solvent was evaporated. The oil was purified by flash chromatography on silica gel using 1% MeOH/$CHCl_3$ as the eluent to receive the pure title product (0.152 mg; 38%).

TLC (2% MeOH/$CHCl_3$), R_f=0.22.

EXAMPLE 3

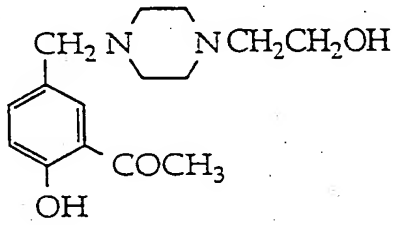
N-(3-Benzyloxycarbonylaminopropyl)-4.5-bis[di(3-(1-hydroxyimino-ethyl)-4-hydroxybenzyl)amino]valerylamide VK-12



A suspension of N-(3-benzyloxycarbonylaminopropyl)-4.5-bis[di(3-acetyl-4-hydroxybenzyl)amino]valerylamide (VK-11) of Example 2 (0.055 g; 0.06 mmol), $NH_2OH \cdot HCl$ (0.042 g; 0.6 mmol) and $NaHCO_3$ (0.055 g; 0.065 mmol) in MEOH (15 ml) was stirred at 65°C for 48 hr. $CHCl_3$ (50 ml) was added to the reaction mixture. The precipitate was filtered off. The solvent was evaporated. The residue was purified by flash chromatography on silica gel using $CHCl_3$ and 5% MeOH/$CHCl_3$ as the eluents. 12 mg (20%) of the product were eluted with 10% MeOH/$CHCl_3$. The product is not soluble in $CHCl_3$. TLC (10% MeOH/$CHCl_3$). R_f = 0.15.

EXAMPLE 4

2-Acetyl-4-[4-(2-hydroxyethyl) piperazin-1-ylmethyl] phenol N-269

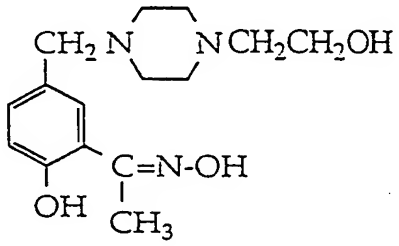


2-piperazin-1-yl-ethanol (260 mg,2 mmole) and 2-acetyl-4-chloromethyl phenol (368 mg, 2 mmole) were stirred in chloroform at room temperature. Sodium carbonate (106 mg, 1 mmole) was added and the reaction mixture was stirred overnight. The solid was filtered off and the organic layer washed with water followed by brine, dried over sodium sulfate, filtered and evaporated to obtain the crude product which was crystallized from ethyl acetate-hexane to receive the title product as yellowish-white crystals (400 mg, 72%), mp= 72-5°C. $C_{15}H_{22}N_2O_3$ requires : N 10.06 found : N 9.70.

^{1}NMR : d ($CDCl_3$) = 12.22 (S, 1H, PhOH), 7.65 (d, 1H, J=1.99 Hz, Ph); 7.45 (dd, 1H, J_1=8.62 Hz, J_2=2.18 Hz, Ph); 6.94 (d, 1H, J= 8.48 Hz, Ph); 3.62 (t, 2H, J=5.25 Hz, CH_2OH); 3.46 (S, 2H, $PhCH_2$); 2.65 (S, 3H, $COCH_3$); 2.57-2.41 (m, 11H, CH_2x5+ OH).

EXAMPLE 5

2-(1-Hydroxyiminoethyl)-4-[4-(2-hydroxyethyl)piperazin-1-ylmethyl] phenol N-275



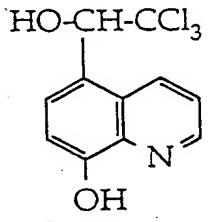
Hydroxylamine hydrochloride (63 mg, 0.9 mmole) and sodium bicarbonate (76 mg, 0.9 mmole) were dissolved in distilled water (1 ml). 2-Acetyl-4-[4-(2-hydroxyethyl)piperazin-1-ylmethyl]phenol (85 mg, 0.3 mmole) in absolute methanol (2 ml) was added and the reaction mixture was stirred at 65°C for 24 h. $CHCl_3$ (20 ml) was then added, the organic phase washed with water followed by brine, dried over Na_2SO_4, filtered and evaporated to obtain the title product (52 mg, 81%).

^{1}NMR : d ($CDCl_3$) = 7.36 (d, 1H, J=1.94 Hz, **Ph**); 7.15 (dd, 1H, J_1=2.0 Hz, J_2=8.29 Hz, **Ph**); 6.87 (d, 1H, J=8.29 Hz, **Ph**); 3.65 (t, 2H, J=5.3 Hz, **CH_2OH**); 3.52 (S, 2H, Ph**CH_2**); 2.60 (t, 10H, J=5.4 Hz, **CH_2x5+1H, OH**); 2.31 (S, 3H, **CH_3**).

EXAMPLE 6

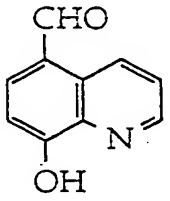
5-Formyl-8-quinolinol VK-5 (VK-56)

I. 5-(2,2,2-trichloro-1-hydroxyethyl)-8-quinolinol.



To trichloracetaldehyde (41.6 g; 0.28 mole) was added conc. H_2SO_4 (1 drop) and the mixture was mixed. This chloral was decantated (without the acid) into 8-quinolinol (27.17 g; 0.187 mole). Reaction was exotermic. After few minutes of mixing the reaction mixture was left standing for 3 days at room temperature until it turned to a light yellow solid. It was stirred at 65-70°C in silicon oil bath for 35 hrs. After cooling the reaction mixture was stirred with 3N hydrochloric acid (470 ml; 140 ml 32% HCl + water --- 470 ml) at 80°C for 1.5 hr (using mechanical stirrer) until the orange reaction mass completely turned to yellow crystalline hydrochloride which was filtered after cooling. The crystals were suspended in hot water (375 ml) and sodium acetate trihydrate (75 g; 0.55 mole) was added to the suspension. The mixture was stirred on a water bath (80°C) for 30 min. The resulting orange-yellow free base was filtered after cooling and washed with hot water and dried under high vacuum with P_2O_5. Yield 44.0 g (80%). (from Bull. Chem. Soc. Jp. 42:1741 (1969).

II. 5-Formyl-8-quinolinol

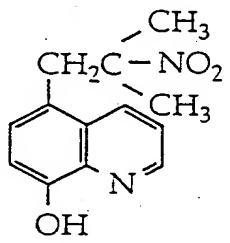


Analytic acetone (220 ml) was added to a 3-necked flask (1 l) equipped with mechanical stirrer which was placed in dry ice-acetone bath, under Ar. Na (4.5 g; 0.2 mole) was added to the cooled acetone during 30 min, then 5-chloralyl-8-quinolinol (12.0 g; 0.041 mole) was added to the acetone suspension and the resulting mixture was stirred for 2-3 hr at 25°C. After standing for 3 days at room temperature the resulting precipitate was filtered in buchner, washed with acetone and dried by air. Then the precipitate was dissolved in water (100 ml) and was treated by charcoal (2 teaspoons). After filtration, the solution was neutralized with a 50% solution of CH_3CO_2H (few drops). A straw yellow precipitate was filtered (mother solution 1) and dried in a desiccator over P_2O_5 to receive 3.2 g. A mixture of this precipitate (3.2 g) and sodium disulfite (10.4 g; 54.7 mmole) was well stirred in water (21 ml) at 60°C using magnetic stirrer (with charcoal: 2 teaspoons). After cooling, the mixture was filtered and the precipitate washed with water. Concentrated hydrochloric acid (35 ml) was added to the combined filtrate and washings, and the solution was stirred with heating until the evolution gas SO_2 ceased. Then the solution was concentrated to get solid + solution (10 ml). After standing overnight the separated solid was filtered, dissolved in hot water (70 ml) and the solution was treated with charcoal and then filtered. Upon addition of $NaOAc.3H_2O$ (4.2 g) to the filtrate the free base

separated, which was filtered and washed with water. Yield: 1.0g. It was recrystallized from benzene to form almost colorless prisms. M.p. 177-8°C (in capillary).

EXAMPLE 7

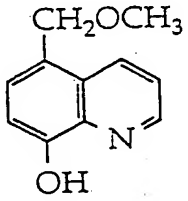
5-(2-Methyl-2-nitropropyl)-8-quinolinol VK-8



A solution of 2-nitropropane (30 ml, 0.33 mmole) in DMF (20 ml) was added to a mixture of 5-chloromethyl-8-quinolinol hydrochloride (3g; 13 mmole) and potassium-tert-butoxide (5.6 g, 50 mmole) at 5°C under Ar atmosphere. The reaction mixture was stirred for 24h at room temperature. $CHCl_3$ (100 ml) was then added, and the solution was washed with water until a neutral pH was obtained. It was then washed with brine, dried over Na_2SO_4 and evaporated to dryness under vacuum (50°C/1 mm/Hg). The residue was crystallized from ethanol (50 ml) yielding 1.4g (43%) of the title product. M.p. 133-134°C; TLC ($CHCl_3$/MeOH/NH_3 - 8:2:0.5). R_f = 0.8.

EXAMPLE 8

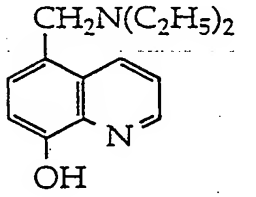
5-Methoxymethyl-8-quinolinol VK 62



5-Chloromethyl-8-quinolinol hydrochloride (2.145g; 9.3 mmole) was added to a mixture of sodium methoxide (1.763g; 32.6 mmole) in MeOH (40 ml). The reaction mixture was stirred for about 4h at room temperature. The mixture was evaporated to dryness. The residue was dissolved in $CHCl_3$ (100 ml) and the solution was washed with water until a neutral pH was obtained. It was then washed with brine, dried over Na_2SO_4 and evaported to dryness. The residue was extracted with hexane (100 ml). The hexane solution was evaporated to give the title product, 0.36 g (20%). M.p. 75-76°C. TLC ($CHCl_3$/MeOH/NH_3 · 9.5 : 0.5 : 0.1). R_f = 0.36.

EXAMPLE 9

Synthesis of 5-diethylaminomethyl-8-quinolinol VK-64

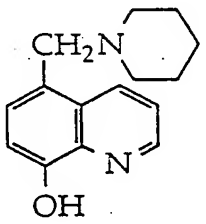


Diethylamine (2.4 ml; 23.2 mmole) was added to a mixture of

5-chloromethyl-8-quinolinol hydrochloride (2.131 g; 9.25 mmole) in $CHCl_3$ (50 ml) at 5°C. The reaction mixture was stirred for 24 h at room temperature. $CHCl_3$ (50 ml) was then added and the solution was washed with 5% $NaHCO_3$ (2x50 ml) and brine (50 ml) and dried over Na_2SO_4. The solution was filtered and evaporated to dryness. The residue was crystallized from hexane (~10-15 ml) and gave 1.23 g (58%) of the product. An analytic sample of the title product was obtained by sublimation (80°C/1 mm Hg). M.p. = 71-72°C.

EXAMPLE 10

Synthesis of 5-piperidinomethyl-8-quinolinol VK-63



Piperidine (2 ml; 20.26 mmole) was added to a solution of 5-chloromethyl-8-quinolinol (1.87 g; 8.13 mmole) in $CHCl_3$ (50 ml) at 5°C. The mixture was stirred for two days at room temperature. Then the mixture was evaporated under vacuum to dryness. The residue was dissolved in $CHCl_3$, washed with 5% $NaHCO_3$ (2x50 ml), followed by brine (50 ml), dried over Na_2SO_4 and evaporated to dryness. The residue was crystallized from hexane to give 1.0 g of the title product (50%). M.p. 96°C. TLC ($CHCl_3$; MeOH; NH_3 = 8:2:0.5). R_f = 0.63.

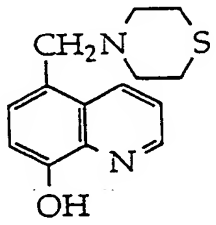
EXAMPLE 11

Synthesis of 5-morpholinomethyl-8-quinolinol VK-61

Morpholine (1.9 ml; 21.8 mmole) was added to a solution of 5-chloromethyl-8-quinolinol (1.918 g; 8.34 mmole) in $CHCl_3$ (50 ml) at 5°C. The reaction mixture was stirred overnight at room temperature. Then $CHCl_3$ (100 ml) was added and the solution was washed with 5% $NaHCO_3$ (2x50 ml), followed by brine (50 ml), and dried over Na_2SO_4. The solution was filtered and evaporated under vacuum to dryness. The residue was crystallized from hexane-$CHCl_3$ and gave 1.2g (59%) of the title product. M.p. 130°C. TLC ($CHCl_3$; MeOH; NH_3 = 8:2:0.5). R_f = 0.69.

EXAMPLE 12

Synthesis of 5-thiomorpholinomethyl-8-quinolinol VK-67

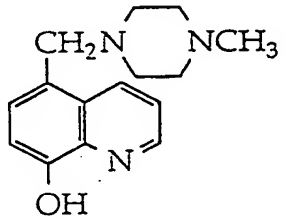


Thiomorpholine (1 ml; 10 mmole) was added to a solution of 5-chloromethyl-8-quinolinol hydrochloride (2.3 g; 10 mmole) and diisopropylethlamine (3.5 ml; 20.1 mmole) in $CHCl_3$ (50 ml) at

5°C. The reaction mixture was stirred for 24 h at room temperature. $CHCl_3$ (50 ml) was then added and the solution was washed with 5% $NaHCO_3$ (2x50 ml) and brine (50 ml) and dried over Na_2SO_4. The solution was filtered and evaporated to dryness. The residue was crystallized from hexane-$CHCl_3$ and gave 1.5 g (58%) of the title product. M.p. = 121-122°C.

EXAMPLE 13

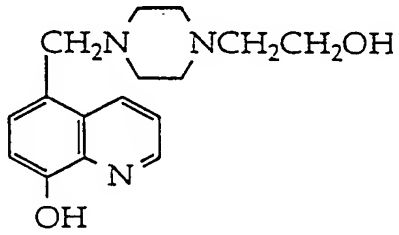
Synthesis of 5-(4-methylpiperazinomethyl)-8-quinolinol VK-70



N-methylpiperazine (5.0 ml, 45 mmole) was added to a mixture of 5-chloromethyl-8-quinolinol hydrochloride (4.1 g, 17.8 mmole) in $CHCl_3$ (80 ml) at 5°C. The mixture was stirred for 24 h at room temperature. $CHCl_3$ (100 ml) was then added and the solution was washed with 5% $NaHCO_3$ (3x50 ml) and brine (2x50 ml) and then dried over Na_2SO_4. The solution was filtered and evaporated to dryness. The residue was crystallized from a mixture of benzene-hexane and gave 2.89 g (63%) of the title product. M.p. 126-127°C. TLC ($CHCl_3$-MeOH-NH_3 9:1:0.1) R_f=0.35.

EXAMPLE 14

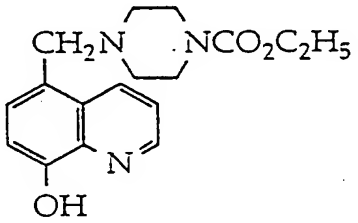
5-(4-(2-Hydroxyethyl)piperazin-1-ylmethyl)-quinolin-8-ol VK-28



Piperazinethanol (7.2 ml; 58.7 mmol) was added to a suspension of 5-chloromethylquinolin-8-ol (5.413 g; 23.5 mmol) in $CHCl_3$ (80 ml) at 0°C. The mixture was stirred overnight at room temperature. The reaction mixture was subsequently washed with a saturated $NaHCO_3$ solution and brine, then dried with Na_2SO_4 and evaporated to dryness. Crystallization of the residue from a mixture of $CHCl_3$-Hex gave 4.05 g (60%) of title product. M.p. 123-4°C. The mother liquor was evaporated and the residue was crystallized to yield 1.5 g of title product. Overall yield: 5.55 g (82%). A highly pure product was obtained by soxleth extraction using hexane as the extractant. TLC ($CHCl_3$ MeOH NH_3 = 8:2:0.5). R_f = 0.4.

EXAMPLE 15

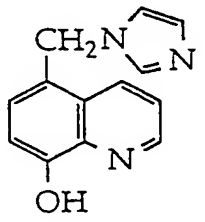
Synthesis of 5-(4-ethoxycarbonylpiperazinomethyl)-8-quinolinol VK-68



N-ethoxycarbonylpiperazine (1.5 ml, 10.2 mmole) was added to a mixture of 5-chloromethyl-8-quinolinol hydrochloride (2.36 g, 10.2 mmole) and diisopropylethylamine (3.6 ml, 20.6 mmole) in $CHCl_3$ (50 ml) at 5°C. The mixture was stirred for 24 h at room temperature. $CHCl_3$ (100 ml) was then added and the solution was washed with 5% $NaHCO_3$ (3x50 ml) and brine (2x50 ml) and then dried over Na_2SO_4. The solution was filtered and evaporated to dryness. The residue was crystallized from a mixture of benzene-hexane and gave 1.38 g (42%) of the title product. M.p. 96°C. TLC ($CHCl_3$-MeOH-NH_3 9:1:0.1) R_f = 0.6; TLC ($CHCl_3$-MeOH-Me_3 9:0.5:0.05) R_f=0.4.

EXAMPLE 16

5-(Imidazol-1-ylmethyl)-8-quinolinol VK 69



A mixture of 5-chloromethyl-8-quinolinol hydrochloride (3.45g; 15 mmole), imidazole (1.02g; 15 mmole) and diisopropyl-ethylamine (5.25 ml; 30 mmole) in $CHCl_3$ (60 ml) was stirred for 24h at room temperature and then for 3h at 60°C. After cooling, the mixture was evaporated, washed with ethyl acetate (50 ml) and then hexane (50 ml). The residue was crystallized from a mixture of toluene and ethanol (abs.) to give 0.83g (29%) of title product. M.p. 182°C.

EXAMPLE 17

Prevention of lipid peroxidation in brain tissue

Brain cortex homogenates (10% wt/vol) from male Wistar rats were prepared in 0.3 M sucrose and incubated in air as described by Rehncrona et al. (1980) J. Neurochem. 34: 1630-38. The 0.1-ml aliquots of homogenate were incubated alone at 30°C for 90 min to determine basal lipid peroxidation, or incubated after the addition of 10^{-4} $Fe_2(SO_4)_3$ and in the presence of 10^{-3} M iron chelator of formula I or II or 10^{-4}M desferrioxamine, for comparison. Lipid peroxidation was assayed by measurement of malondialdehyde formation, as described by Dexter et al. (1989). J. Neurochem. 52: 381-89. The results are expressed as means±SEM.

Statistical analysis was performed by two-tailed Student's *t* tests.

Fig. 1 shows the effect of iron and various novel iron chelators and desferrioxamine (desferal) on lipid peroxidation, as measured by malondialdehyde (MDA) formation in rat cerebral cortex homogenates. The chelators N-269, N-271 and N-275 were not effective in preventing ferric chloride induced lipid peroxidation *in vitro*. In contrast, VK-12, VK-28 and SL-16 reduced iron induced MDA formation (B) by 50% approximately. Desferal was the most efficient chelator in this test. The concentration of each chelator was 10^{-3}M and that of ferric chloride 10^{-4}M.

EXAMPLE 18

Prevention of 6-OHDA-induced toxicity in rats

Out of the six iron chelators examined *in vitro* in Example 17, two different types of chelators, VK-12 and VK-28, which were the most effective in inhibiting MDA formation, were chosen for *in vivo* studies.

The chelators (200 μg) were injected intraventriculary alone or prior to 6-OHDA (250 μg).

Male Sprague-Dawley rats, weighing 230-270 g, were housed in a controlled-temperature room with a standardized dark-light schedule (12/12 h) for 4 weeks. Rats were anesthetized with a mixture of 15 mg/kg of pentobarbital and 60 mg/kg of chloral hydrate. 6-OHDA (250 μg in 5 μl of 0.9% NaCl containing 0.2% ascorbic acid), the chelator (200 μg in 5 μl), a combination of both (the chelator 15 min before 6-OHDA), or saline (5 μl) (control) was injected into the right cerebral ventricle using

stereotactic techniques. The coordinates with bregma as the reference were D 0.8 mm, L 1.3 mm, and V 3.6 mm according to the atlas of Paxinos and Watson. Pargyline (50 mg/kg i.p.) and desmethylimipramine-HCl (25 mg/kg i.p.) were administered to all the rats 60 min before intracerebroventricular injection. Pargyline inhibits monoamine oxidase and thereby enhances the toxicity of 6-OHDA, and desmethylimipramine provides protection for central noradrenergic neurons from the toxin. All the animals received a daily injection of isotonic glucose (4 ml/day i.p.) until they regained their original body weight. Behavioral tests were performed 4 weeks after operation, commencing between 8 and 10 a.m. The rats were killed after the behavioral studies. Desferal was obtained from Ciba Geigy, and other chemicals were from Sigma (St. Louis, MO, U.S.A.).

For behavioral studies, rats were placed on a Varimax activity meter (Columbus Instruments). Horizontal spontaneous locomotor activity in a novel space was measured during the first 5 min. Rearing activity (spontaneous lifting of the two front paws off the cage floor) was determined every fourth minute for 30 min by direct observation by two individuals blind to the treatment.

Norepinephrine (NE), DA, and metabolite levels were measured as follows: four weeks postoperatively rats were killed by decapitation, and the brains were rapidly removed. The striata were dissected on an ice-chilled glass plate and quickly frozen in liquid nitrogen. The endogenous levels of NE, DA, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) were determined by HPLC with electrochemical detection (Ben-Shachar et al. (1991) Eur. J. Pharmacol. 202: 177-83). All data

are expressed as mean±SEM values. Statistical analysis was carried out by analysis of variance with multiple comparisons followed by Student's *t* test.

Striatal dopamine and its metabolites DOPAC and HVA concentrations, which were determined by HPLC, served as a criteria for the extent of the damage caused by 6-OHDA in the presence or absence of the iron chelators. The specificity of the effects of 6-OHDA and the chelators was established by studying the changes in striatal norepinephrine (NE) and serotonine (5-HT) and its main metabolite 5-HIAA (5-hydroxy-indole acetic acid).

Both VK-12 and VK-28 at a dose of 200 μg efficiently prevented the 6-OHDA-induced reduction in striatal dopamine and DOPAC concentrations in the rat. The significant damage caused by 6-OHDA to the nigrostriatal dopamine neurons manifests itself in the increased dopamine turnover which is calculated by the ratio (DOPAC+HVA)/DA. Dopamine turnover was normal in rats pretreated with iron chelators (Table 1).

Table 1: Biogenic amines and their metabolites in the rat striatum after intraventricular injection of 200 μg of chelator prior to 250 μg 6-OHDA

pmol/mg tissue	saline (9)	6-OHDA (9)	VK-28 Comb. (8)	VK-12 Comb. (8)
NE	4.1±0.2	5.0±0.1	5.01±0.3	4.7±0.5
DA	47.4±2.2	19.93±5.0[c]	33.8±4.3	31.84±5.3
DOPAC	2.31±0.06	1.79±0.25[a]	2.45±0.25	2.15±0.28
HVA	1.96±0.08	2.24±0.23	2.67±0.33	2.68±0.43
5-HT	4.50±0.51	4.00±0.35	4.24±0.43	4.40±0.41
5-HIAA	4.10±0.29	3.76±0.20	4.48±0.38	4.60±0.53
(DOPAC+ HAV)/DA	0.09	0.202	0.15	0.15

Number in brackets represents the number of animals in each treatment. Comb. stand for 200 μg of chelators +250 μg 6-OHDA. a-$p<0.05$, b-$p<0.025$, c-$p<0.001$.

Basing on confirmation properties of the two iron chelators, the investigators suggested that VK-28 has a better chance to cross the BBB and continued the studies on this compound. In order to decrease to minimum the possibility of a direct interaction between the chelator and the toxin as a cause for the protection, and to try to find a smaller effective dose of the VK-28, 1 μg was injected intraventricularly prior to the injection of 250 μg 6-OHDA. Table 2 shows that even at this dose VK-28 was effective in preventing 6-OHDA-induced lesion.

Table 2: Biogenic amines and their metabolites in the rat striatum after intraventricular injection of 1 μg of chelator prior to 250 μg 6-OHDA.

pmol/mg tissue	saline (8)	6-OHDA (7)	VK-28 Comb. (8)
NE	1.4±0.1	1.1±0.1	1.3±0.12
DA	59.2±6.4	12.93±3.3[a]	62.9±3.13
DOPAC	2.81±0.5	0.76±0.11[a]	2.49±0.13
HVA	2.67±0.18	1.10±0.21[a]	2.77±0.25
5-HT	3.33±0.53	3.22±0.42	4.84±0.45
5-HIAA	5.29±0.53	6.29±0.65	4.98±0.46
(DOPAC+ HAV)/DA	0.09	0.14	0.08

Number in brackets represents the number of animals in each treatment. Comb. stand for 1 μg of chelators +250 μg 6-OHDA. a-$p<0.001$.

The main goal at this stage of the research was to find out whether VK-28 given peripherally would be able to prevent 6-OHDA-induced toxicity. In other words the question was whether the chelator will stay stable in the periphery, cross the BBB and exert its antidote effect. Rats were daily injected with VK-28 (5 mg/Kg i.p.) for 10 days. Control group received phosphate buffer pH-6.4 0.1 M. On the 11th day the rats of both groups were

injected intraventricularly with 250 µg 6-OHDA. Partial but significant protection against 6-OHDA toxicity was observed with peripheral pretreatment with VK-28 (Fig. 2, Table 3).

Fig. 2 shows dopamine and its metabolites DOPAC and HVA in the striatum of rats chronically treated with VK-28 (5mg/Kg/day i.p.). As expected the neurotoxin 6-OHDA caused a 80% decrease in striatal dopamine levels which was accompanied by a significant decrease in DOPAC and HVA. Intraperitoneal treatment with VK-28 for 10 days before intraventricular injection of 6-OHDA (combination) partially protected the dopaminergic neurons from degeneration as expressed by dopamine, DOPAC and HVA levels.

Table 3: Biogenic amines and their metabolites in the rat striatum after chronic peripheral injection of 5 mg/Kg VK-28 prior to intraventricular injection of 250 µg 6-OHDA

pmol/mg tissue	saline (6)	6-OHDA (7)	VK-28 Comb. (8)
NE	1.09±0.03	1.22±0.04	1.21±0.4
DA	49..2±2.59	9.69±2.63[a]	24.4±4.4[ab]
DOPAC	2.02±0.28	0.51±0.11[a]	1.4±0.25
HVA	2.56±0.22	1.05±0.19[a]	2.28±0.75
5-HT	2.99±0.18	2.60±0.15	2.6±0.31
5-HIAA	1.53±0.09	1.57±0.07	1.59±0.16
(DOPAC+ HAV)/DA	0.09	0.16	0.15

Number in brackets represents the number of animals in each treatment. Comb. stand for chelators (5mg/Kg/day i.p. for 10 days) +250 µg 6-OHDA.
a-$p<0.001$ vs. saline, b-$p<0.01$ vs. 6-OHDA.

Ten other iron chelators were examined for their ability to inhibit lipid peroxidation *in vitro*. Their relative capability to inhibit MDA formation in the presence of 10^{-4} M $FeCl_3$ in rat brain homogenates as compared to that of VK-12, VK-28 and

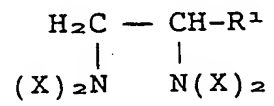
desferrioxamine is summarized in Fig. 3.

Fig. 3 shows the anti-oxidant activity of various novel iron chelators. Ferric chloride (10^{-4}M) induced lipid peroxidation, as measured by MDA formation in rat cerebral cortex homogenates, was inhibited to a different degree by 10^{-3}M of the various chelators. The *in vitro* results may not parallel the *in vivo* anti-oxidant potentials of the chelators but give only an indication of their ability to reduce oxidative stress. Anti-oxidant activity of any drug *in vivo* may be affected by many parameters e.g. the ability to cross membranes, the interaction with surrounding molecules, the local pH and ionic strength etc.

CLAIMS

1. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a compound selected from the group consisting of:

(a) a compound of formula I:



(I)

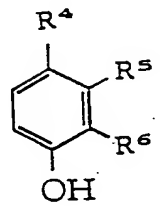
wherein

R^1 is a radical $-(CH_2)_n-CONR^2R^3$ wherein n is an integer from 1 to 20, R^2 is H or hydrocarbyl and R^3 is a hydrophobic radical, and

X is a radical $-CH_2Y$, wherein Y is a radical 3-acyl-4-hydroxyphenyl, 3-hydroxyiminoalkyl-4-hydroxyphenyl, or COOZ, wherein Z is H, alkyl, aryl or aralkyl,

and

(b) a compound of formula II:



(II)

wherein

R^4 is acyl, nitroalkyl, alkoxymethyl or $-CH_2NR^7R^8$, wherein R^7 and R^8 are H or alkyl or together with the N atom

form a saturated or unsaturated 5-6 membered ring optionally containing a further heteroatom selected from N, O or S, the further N atom being optionally substituted, and

either R^5 is H and R^6 is acyl or hydroxyiminoalkyl or R^5 and R^6 together with the phenyl ring form a quinoline, a 1,2,3,4- tetrahydroquinoline or a perhydroquinoline ring, and

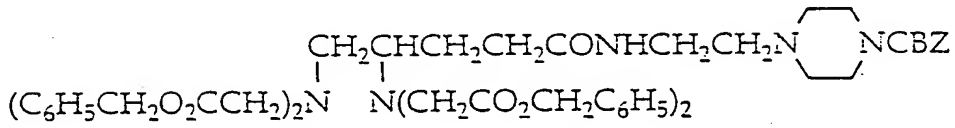
pharmaceutically acceptable salts of the compounds of formulas I and II.

2. A pharmaceutical composition according to claim 1 comprising a compound of formula I in which R^1 is $-(CH_2)_nCONR^2R^3$ wherein n is from 1 to 4, R^2 is H and R^3 is a hydrophobic radical selected from C_6-C_{20} alkyl or alkenyl, aryl, C_5-C_{20} acyl or $-(CH_2)_mCONY_1Y_2$, wherein Y_1 is H or alkyl and Y_2 is benzyloxycarbonyl, or Y_1 and Y_2 together with the N atom form a saturated 5-6 membered ring optionally containing a further heteroatom, and when said further heteroatom is N it may be optionally substituted.

3. A pharmaceutical composition according to claim 2 wherein n is 2, R^2 is H and Y_1 and Y_2 together form a piperazine ring substituted at the N-atom by a carbobenzoxy radical.

4. A pharmaceutical composition according to any one of claims 1 to 3 wherein X is $-CH_2Y$ in which Y is 3-acetyl-4-hydroxyphenyl, 3-hydroxyiminoethyl-4-hydroxyphenyl, or $-COOCH_2C_6H_5$.

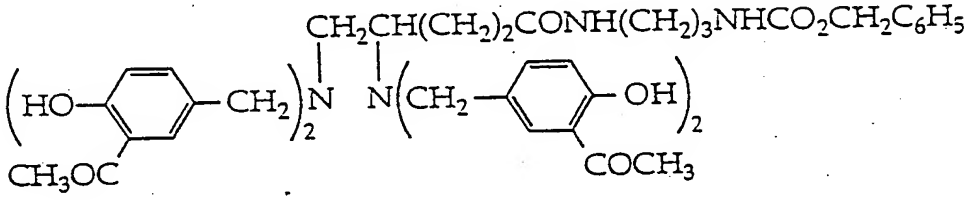
5. A pharmaceutical composition according to claim 1 comprising a compound of the formula



(SL-16)

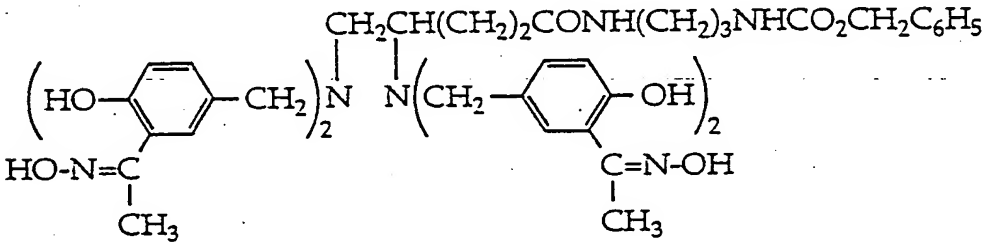
in which CBZ is a carbobenzoxy radical.

6. A pharmaceutical composition according to claim 1 comprising a compound of the formula



(N-271)

7. A pharmaceutical composition according to claim 1 comprising a compound of the formula

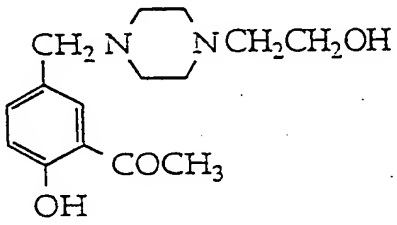


(VK-12)

8. A pharmaceutical composition according to claim 1 comprising a compound of formula II in which R^5 is H and R^6 is acyl or hydroxyiminoalkyl.

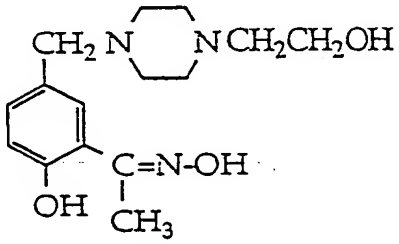
9. A pharmaceutical composition according to claim 8 comprising a compound of formula II in which R^4 is a radical $-CH_2NR^7R^8$ wherein R^7 and R^8 form with the N atom a 4-substituted piperazine ring.

10. A pharmaceutical composition according to claim 8 or 9 comprising a compound of the formula



(N-269)

11. A pharmaceutical composition according to claim 8 or 9 comprising a compound of the formula



(N-275)

12. A pharmaceutical composition according to claim 1 comprising a compound of formula II in which R^5 and R^6 together with the phenyl ring form a quinoline ring.

13. A pharmaceutical composition according to claim 12 wherein R^4 is acyl.

14. A pharmaceutical composition according to claim 13 comprising the compound 5-formyl-8-quinolinol.

15. A pharmaceutical composition according to claim 12 wherein R^4 is nitroalkyl.

16. A pharmaceutical composition according to claim 15 comprising the compound 5-(2-methyl-2-nitropropyl)-8-quinolinol.

17. A pharmaceutical composition according to claim 12 wherein R^4 is alkoxymethyl.

18. A pharmaceutical composition according to claim 17 comprising the compound 5-methoxymethyl-8-quinolinol.

19. A pharmaceutical composition according to claim 12 wherein R^4 is $-CH_2NR^7R^8$ and R^7 and R^8 are both lower alkyl.

20. A pharmaceutical composition according to claim 19 comprising the compound 5-diethylaminomethyl-8-quinolinol.

21. A pharmaceutical composition according to claim 12

wherein R^4 is $-CH_2NR^7R^8$ and R^7 and R^8 together with the N atom form a saturated 6-membered ring optionally containing a further heteroatom selected from O, S or N, and when the further heteroatom is N it may be optionally substituted.

22. A pharmaceutical composition according to claim 21 comprising a compound selected from:

5-piperidinylmethyl-8-quinolinol (VK-63)

5-morpholinylmethyl-8-quinolinol (VK-61)

5-thiomorpholinylmethyl-8-quinolinol (VK-67)

5-(4-methylpiperazinylmethyl)-8-quinolinol (VK-70)

5-[4-(2-hydroxyethyl)piperazinylmethyl]-8-quinolinol (VK-28)

and 5-[4-ethoxycarbonylpiperazinylmethyl)-8-quinolinol (VK-68)

23. A pharmaceutical composition according to claim 12 wherein R^4 is $CH_2NR^7R^8$ and R^7 and R^8 together with the N atom form an unsaturated 5-membered ring containing two N atoms.

24. A pharmaceutical composition according to claim 23 comprising the compound 5-(imidazol-1-ylmethyl)-8-quinolinol.

25. A pharmaceutical composition according to any one of claims 1 to 24 useful to prevent lipid peroxidation in the brain of mammals.

26. A pharmaceutical composition according to any one of claims 1 to 25 for the treatment of stroke and Parkinson's disease.

27. Use of a compound of formula I or formula II in claim 1 to prevent lipid peroxidation in the brain of mammals for the preparation of pharmaceutical compositions for the treatment of stroke.

28. Use of a compound of formula I or formula II in claim 1 as neuroprotective iron chelators for the preparation of pharmaceutical compositions for the treatment of Parkinson's disease.

29. Use of a compound of formula I or formula II in claim 1 as neuroprotective iron chelators for the preparation of pharmaceutical compositions for the treatment of stroke.

30. A compound of formula I in claim 1.

31. A compound of formula I as defined in any one of claims 1 to 7.

32. A compound of formula II in claim 1, excepting the compounds 5-formyl-8-quinolinol and 5-methoxymethyl-8-quinolinol.

33. A compound of formula II as defined in any one of claims 8 to 11.

34. A compound of formula II as defined in any one of claims 12, 13, 15-17, and 19-24, excepting the compounds 5-formyl-8-quinolinol and 5-methoxymethyl-8-quinolinol.

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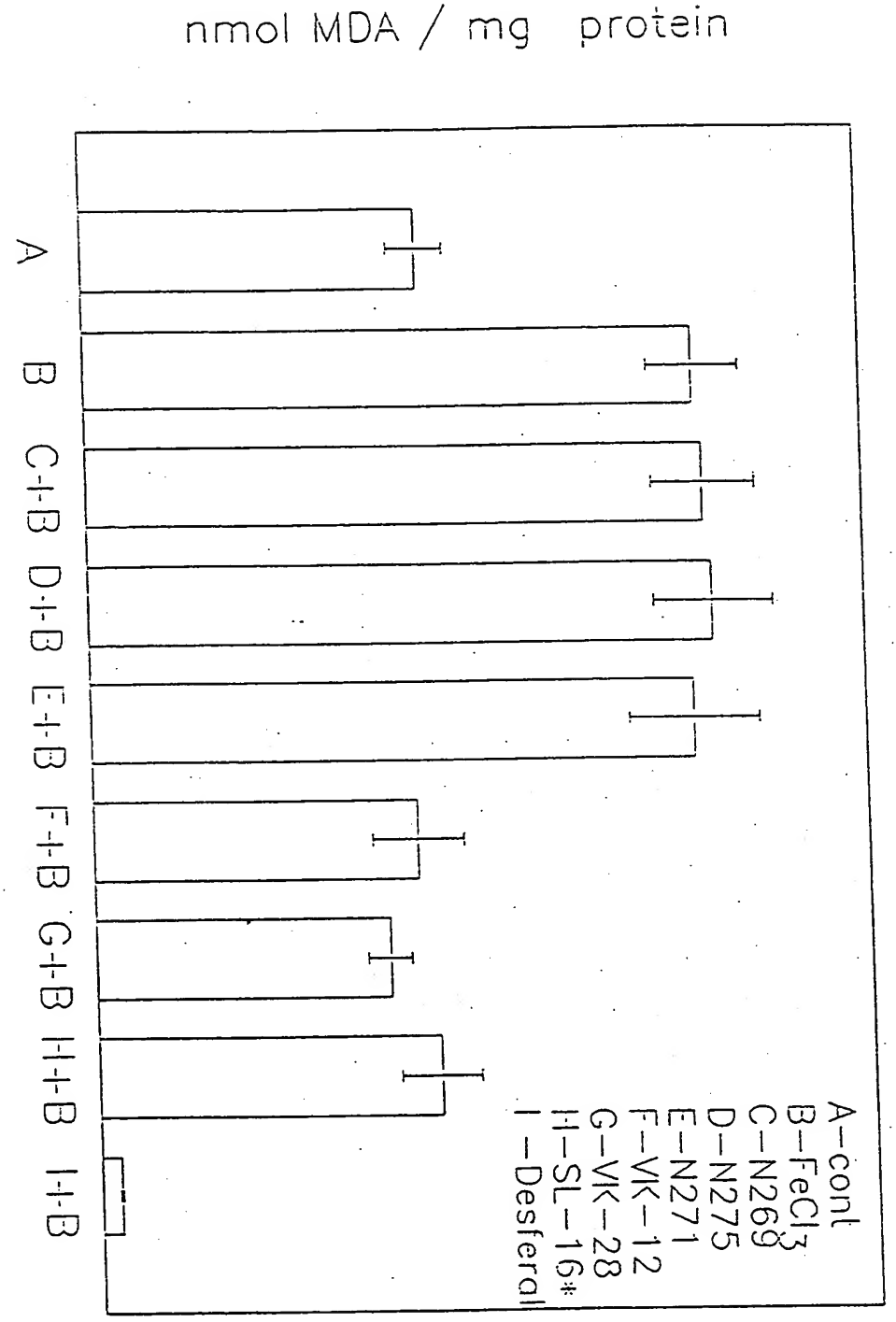

nmol MDA / mg protein
A
B
C+B
D+B
E+B
F+B
G+B
H+B
I+B
A-cont
B-FeCl3
C-N269
D-N275
E-N271
F-VK-12
G-VK-28
H-SL-16*
I-Desferal

Fig. 1

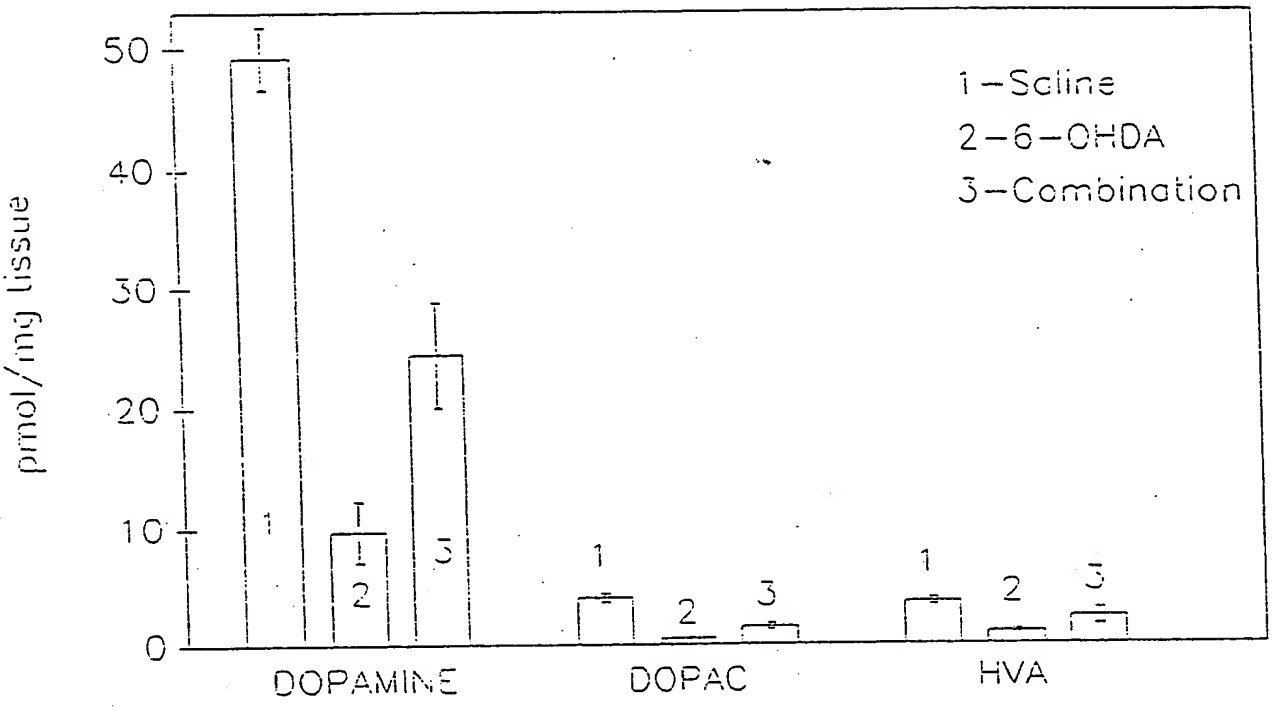
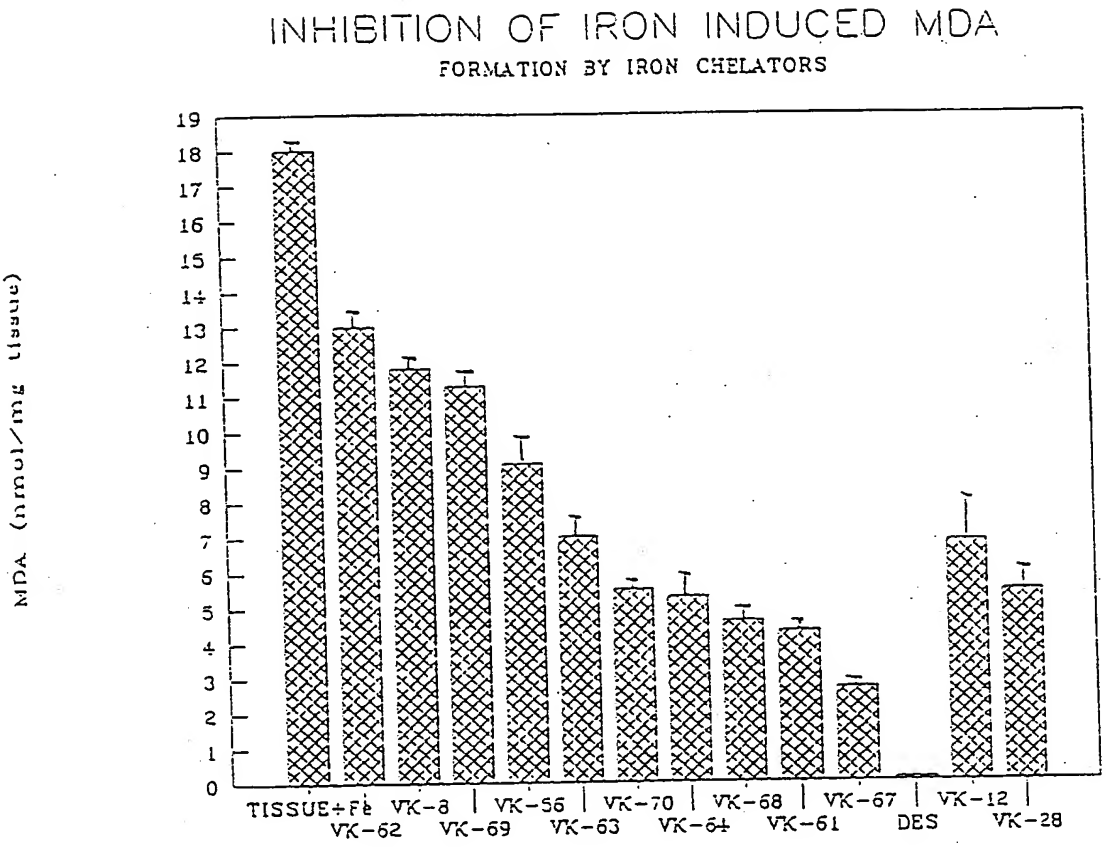

pmol/mg tissue
50
40
30
20
10
0
1-Saline
2-6-OHDA
3-Combination
1
2
3
DOPAMINE
DOPAC
HVA

Fig. 2



Chelator 10^{-3}M

$FeCl_3$ 10^{-4}M

Fig. 3